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THE VALUE OF RADIOTHERAPY IN MEDIASTINAL TUMORS*

By ARTHUR U. DESJARDINS, M. D.
Rochester, Minnesota

MEDIASTINAL tumors often constitute a difficult problem in diagnosis as well as in treatment. Such neoplasms may assume considerable dimensions before the patient is aware that his health is deteriorating or even before any symptoms make their appearance. Pain is the symptom which causes most patients to consult a physician, but many tumors originate in the mediastinal structures and do not cause pain until they have attained sufficient size to interfere with respiration, circulation, or deglutition, and even then many mediastinal growths are essentially painless. Therefore, the early recognition of such neoplasms, so significant in treatment, is not so simple as it may appear. Moreover, the importance for the physician to know the character of such tumors is as great as his ability to obtain such knowledge may be difficult. The clinical manifestations may lead the physician to suspect a tumor, but the physical signs may give an inadequate notion of its size and situation. Roentgenologic examination of the intrathoracic structures may usefully supplement the physical manifestations or give indispensable information about the size and situation of the tumor, and may even give a strong clue to its character, but only too often such information is inadequate or cannot be trusted implicitly. That is, although the roentgenologic examination may clearly and accurately show the outlines of the tumor it cannot be relied on to furnish conclusive evidence of the pathologic character of the growth. When such neoplasms have metastasized to accessible groups of lymph nodes, biopsy may solve the diagnostic problem, but when such metastasis has not occurred this valuable, although not infallible, source of information cannot be utilized.

DIAGNOSTIC VALUE OF RAY THERAPY

It is generally assumed that the value of radiotherapy, as the term implies, is limited to the treatment of malignant and other lesions, but, as will be shown presently, this is not the case. Besides its strictly therapeutic value, the effect of roentgen or radium irradiation on mediastinal as well as other neoplasms may furnish invaluable diagnostic indications, and such indications may often be as conclusive as the microscopic inspection of tissue excised from the tumor. To those who are unfamiliar with the action of roentgen and radium rays on normal and pathologic tissues this statement may appear revolutionary until attention is drawn to one or two important considerations. Usually the pathologist must base his opinion of the character of a tumor on the microscopic appearance of one or several small sections of tissue from one or more parts of the growth. Yet, as is well known, different parts of many neoplasms vary much in architecture and cellular morphology. When a tumor is irradiated, on the other hand, the entire neoplasm is exposed to the influence of the rays, and relatively homogeneous tumors made up largely of one kind of cell retrogress at a specific rate and in a specific manner according to the degree of sensitiveness of the cells. Moreover, the rate and manner of regression of a tumor agree closely with the known radiosensitiveness of its normal cellular prototypes. Different tumors of the same kind often exhibit variations in reaction, but only occasionally is the range of such variation sufficient to cause confusion.

LAW OF SPECIFIC RADIOSENSITIVENESS OF CELLS

Perhaps no law in radiology or in general medicine is more firmly established than the law of the specific radiosensitiveness of cells. Numerous experiments on animals and abundant clinical evidence have proved beyond doubt that every variety of cell in the body and every organ or structure composed largely of one variety of cell has a specific sensitiveness to roentgen or radium rays. The investigations of Heineke, Thies, Warthin, Krause and Ziegler, Rudberg, Aubertin and Bordet, Arella, Regaud and Crémieu, Pappenheim and Plesch, Lazarus-Barlow, and many others have conclusively shown that the lymphocytes in the spleen, lymph nodes, intestinal lymph follicles, bone marrow, circulating blood, and thymus gland are the most sensitive cells in the body. Large numbers of such cells are destroyed within a few days even after moderate irradiation, and such destruction begins within half an hour after exposure to the rays. The rays appear to act first on the nucleus which begins to disintegrate and break up into fragments, and the chromatin débris from the destroyed cells is taken up by some of the reticular cells, which thus assume a phagocytic property and appear to digest the fragmented nuclear chromatin of the destroyed

* From the Section on Therapeutic Radiology, The Mayo Clinic, Rochester, Minnesota.

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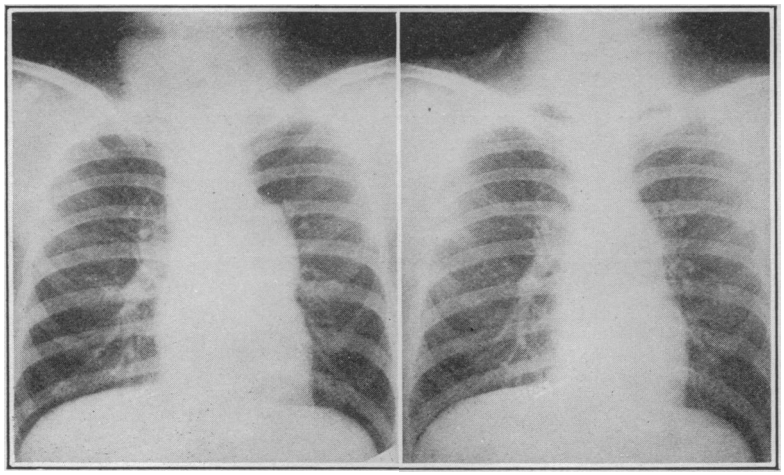

Fig. 1.—Roentgenogram made February 3, 1930, showing a large tumor, apparently originating in the mediastinal lymph nodes.

Fig. 2.—Roentgenogram of the patient, shown in Figure 1, made three weeks after a course of roentgen irradiation and showing marked regression of the mediastinal lymphadenopathic tumor.

lymphocytes. Some of the cells are injured and mitotic division is inhibited without actual disintegration; such cells may regenerate after a time. The degree of lymphocytic destruction and the rate at which the other injured cells regenerate subsequently have been shown to vary according to the dose of rays to which the affected structures have been exposed.

Next in sensitiveness to irradiation are the basal epithelial cells of the salivary glands, the spermotogonial epithelium of the testis and the follicular epithelium of the ovary, the lining epithelium of the upper part of the small intestine, the basal epithelium of the skin and mucous membranes, the peritoneum, and the pleura and lungs. Among the less sensitive structures are the kidneys, liver, and heart, and the least sensitive tissues are those which make up bone and the nervous system. Knowledge of the specific radiosensitiveness of different varieties of normal cells often enables the expert radiologist to identify certain tumors by their rate and degree of regression after exposure to the rays, and such knowledge is of the greatest value in relation to mediastinal tumors. As might be expected, the significance of such knowledge is greatest in relation to tumors derived from the more sensitive varieties of cells. Thus neoplasms originating in lymphoid organs or structures and made up largely of lymphocytes can readily be distinguished by their characteristic and exceptional radiosensitiveness. The reaction of such tumors is usually so great, and corresponds so closely to that if normal lmphocytes, that irradiation constitutes a valuable diagnostic procedure, because it permits the identification of such tumors aside from any difference in their clinical features. Mediastinal tumors derived from epithelial cells, such as epithelioma of the trachea, bronchus, or esophagus, or from connective tissue cells, such as sarcoma (except lymphosarcoma, which is composed chiefly of lymphocytes) are so much more resistant to irradiation that the differentiation of lymphoblastomatous growths from other mediastinal neoplasms seldom presents any difficulty.

COMMENTS ON ILLUSTRATIONS

A few examples may best serve to make clear the value of radiotherapy as a diagnostic test. Figure 1 shows a large mediastinal tumor before the patient had received any treatment. The association of moderate cervical and axillary lymphadenopathy indicated lymphoblastoma, but in the absence of biopsy such a diagnosis rested only on what might be termed circumstantial evidence. Figure 2 shows the mediastinum of the same patient twenty-seven days later or three weeks after a single course of roentgen-ray treatment which required five days, and only part of which was directed to the mediastinal tumor. Such rapid regression of the growth unmistakably points to a lymphoid neoplasm, the seat of which was in the mediastinal lymph nodes. Epithelioma of the bronchus or esophagus as well as other tumors which not infrequently metastasize to the mediastinal nodes never recedes so much in such a short time. The only exceptions are the embryonal carcinoma and the mixed, or teratoid, tumors of the testis which sometimes invade the mediastinal nodes secondarily and also retrogress rapidly under irradiation, but the difference in

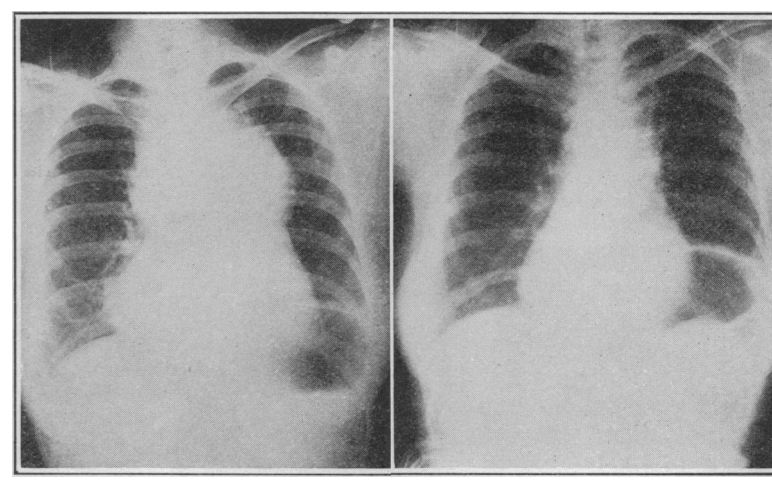

Fig. 3.—Roentgenogram made September 2, 1929, showing a large bilateral mediastinal tumor.

Fig. 4.—Roentgenogram of the patient, shown in Figure 3, made about seven weeks after a course of roentgen irradiation and showing pronounced reduction in size of the mediastinal tumor.

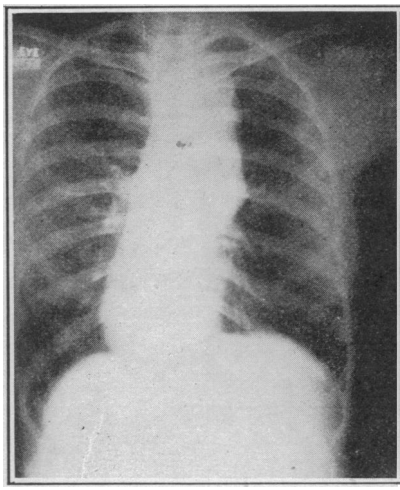

Fig. 8.—Roentgenogram made July 29, 1921, showing mediastinal tumefaction, especially on the right side. This was associated with enlargement of the cervical and axillary lymph nodes.

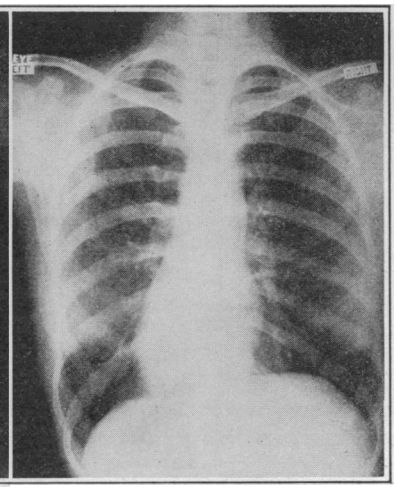

Fig. 9.—Roentgenogram of the thorax, shown in Figure 10, made March 28, 1922, showing complete disappearance of the mediastinal tumor. A roentgenogram made September 28, 1921, had presented the same appearance.

clinical and physical manifestations is usually such that confusion can rarely occur.

Figure 3 shows another large tumor apparently originating in the mediastinum before treatment. Figure 4 shows the marked regression of the neoplasm which occurred during the next eight weeks or within seven weeks after an initial course of roentgen irradiation requiring six days of treatment. Such rapid reduction in the size of the tumor constitutes an absolute indication of a growth derived from lymphoid tissue and composed largely of lymphocytes. No other kind of tumor, with which this could be confused, could retrogress so rapidly. This rapid rate of regression characterizes tumors originating in lymphoid tissue and corresponds so closely to the radiosensitiveness of normal lymphocytes as to furnish an invaluable means of identifying such growths. The difference in the rate of regression between lymphoid and epithelial or connective tissue tumors is so great and so distinct as to leave no room for doubt, and this regardless of the grade of malignancy of the epithelioma or sarcoma. The only exception, and such exceptions are decidedly uncommon, is found in those rare cases in which excessive and abnormal cellular hyperplasia in the enlarged lymph nodes is complicated by secondary infection. The inflammatory process in such cases may greatly alter the reaction of the lymphocytes, and the rate of regression under such conditions may be reduced sufficiently to make absolute differentiation difficult.

The exceptional radiosensitiveness of lymphocytes and of mediastinal and other tumors derived from such cells also makes it possible to distinguish growths of this character from lesions such as aneurysm of the aorta. The differential diagnosis of aneurysm may be difficult, and the deduction from roentgenologic appearances alone that the condition is aneurysm may often be unreliable. Exposure of the mediastinum to an adequate but moderate dose of roentgen rays is an almost infallible means of ascertaining whether an abnormal mediastinal shadow is caused by a lymphoid tumor or by an aortic aneurysm. In the case of the former the shadow will rapidly diminish in size, but in the case of the latter the shadow will remain unchanged. In other words, the lymphadenopathy will promptly show the influence of exposure to

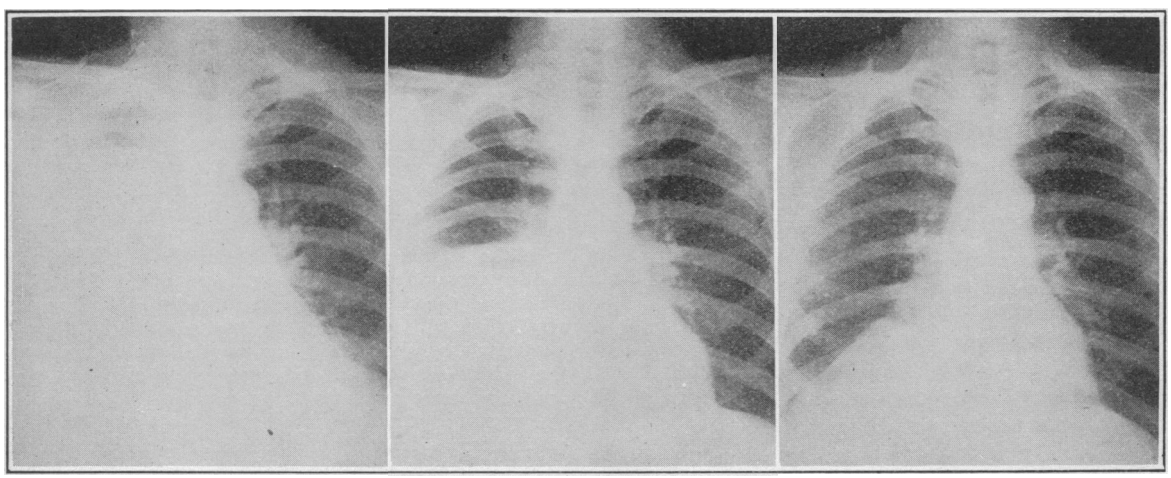

Fig. 5.—Roentgenogram made March 10, 1925, showing practically complete right hydrothorax, indicating circulatory obstruction caused by enlarged mediastinal lymph nodes.

Fig. 6.—Roentgenogram of the thorax, shown in Figure 5, made April 7, 1925, showing beginning absorption of the remaining fluid in the right pleural cavity as the lymphadenopathy receded after removal of 2700 cubic centimeters of clear fluid on March 30, 1925.

Fig. 7.—Roentgenogram of the thorax, shown in Figures 5 and 6, made May 25, 1925, showing complete absorption of the fluid from the right pleural cavity.

the rays, while the aneurysm will not be affected in the least.

Sometimes the diagnostic problem may be to decide between a malignant tumor and a benign, inflammatory process. Again radiotherapy may furnish an important clue. Inflammatory lesions confined to the mediastinum and contiguous structures may differ considerably according to the identity of the infecting organisms, and they may vary much in the degree of leukocytic infiltration. Some degree of infiltration, however, is usually present. It is well known that the majority of leukocytes infiltrating such lesions are lymphocytes, at least at a certain stage, and it may safely be assumed that the infiltrating lymphocytes will be destroyed by irradiation. The effectiveness of radiotherapy for numerous acute and chronic forms of inflammation, such as furuncle, carbuncle, delayed resolution in pneumonia, trachoma, erysipelas, parotitis, tuberculous adenitis and peritonitis, and actinomycosis, rests on such vulnerability of the leukocytes and especially of lymphocytes. Therefore, if a mediastinal lesion reacts at the rate of normal lymphocytes and if the clinical features are distinctly not those of lymphoblastoma, it may confidently be assumed that the lesion represents some variety of inflammation and not a malignant condition. Such reaction probably explains the exceptionally prompt disappearance, under small doses of roentgen rays, of lesions previously assumed to be malignant.

THERAPEUTIC VALUE

As may be surmised from the foregoing considerations on the diagnostic possibilities of radiotherapy, the value of roentgen-ray or radium treatment for mediastinal tumors is greatest in neoplasms derived from and composed of cells which have a high degree of radiosensitiveness, such as the lymphadenopathic growths which typify Hodgkin's disease, lymphatic leukemia, and lymphosarcoma. Unfortunately, the cause of these diseases, or of these different phases of the same pathologic condition, is not yet known, and the ultimate prognosis is almost always unfavorable. It is true that an occasional case of Hodgkin's disease is discovered and treated early and that a permanent cure sometimes results, but such exceptions are so infrequent as to emphasize the rule. Desjardins and Ford (1923) established the fact that the duration of the disease in the average case, without systematic treatment, is approximately two and a half years. Even though, when the disease is allowed to develop without any attempt at therapeutic control, the outlook for the patient is decidedly unpromising and the physical status deteriorates more or less steadily, adequate treatment may alter the situation greatly and the improvement may be maintained for months or years. Enormous mediastinal tumors of this character interfering with respiration or circulation and causing cough, dyspnea, shortness of breath, engorgement and dilatation of the superficial veins, and unilateral or bilateral hydrothorax, can often be made to disappear and the general condition to improve in proportion. The rapidity with which even marked symptoms begin to subside after exposure to a suitable dose of radiation is a salient and characteristic feature. The respiratory disturbances and the hydrothorax diminish as the pressure produced by the enlarged mediastinal nodes is relieved. The anemia and pruritus, which so often accompany Hodgkin's disease and lymphosarcoma, promptly subside or disappear in many cases. The effectiveness of the treatment, however, depends to a considerable degree on the extent, degree of chronicity, and stage of the disease. As the lymphoblastomatous process becomes general, it tends to reach what may be designated as a critical point. Sufficient experience with the disease enables one to recognize that the patient has reached or is approaching this stage. The importance of such recognition cannot be overemphasized because, instead of improving the condition of the patient, excessive or too concentrated treatment at or near the critical point may shorten rather than lengthen life. This phase of the disease is related more to the course than to the extent of the condition. In some patients the disease may be extensive, the symptoms pronounced and the patient apparently not far from death, and yet recovery may be possible.

ILLUSTRATIVE CASES

Case 1.—A man, age forty-nine years, registered at the clinic February 18, 1925. He had been bedridden, suffered from extreme dyspnea, and appeared nearly moribund. To his own knowledge he had been a victim of Hodgkin's disease for several years. From time to time, when his general condition had begun to depreciate, he had gone to a local radiologist and received roentgen-ray treatment, after which his condition had improved for a time. In 1924 he had been well enough to play through a strenuous series of tennis championship matches. Only two months before he had regarded himself as fairly well, and yet when he arrived at the clinic he was extremely ill.

The cervical, axillary, inguinal, and even the retroperitoneal lymph nodes were enormously enlarged. A roentgenologic examination of the thorax showed a practically complete right hydrothorax (Fig. 5), indicating associated mediastinal lymphadenopathy and undoubtedly accounting for the dyspnea. The patient's condition was so low, indeed, that the advisability of roentgen-ray treatment was questioned.

However, it was felt that withdrawal of the fluid by thoracentesis might relieve the dyspnea sufficiently to make treatment possible. Accordingly, 2700 cubic centimeters of clear fluid were removed March 11, 1925, and the respiratory difficulty diminished materially (Fig. 6). Roentgen-ray treatment was then inaugurated by short daily sessions to avoid overtaxing the patient's strength. After seven days of treatment another thoracic roentgenogram (Fig. 7) showed that the remaining fluid was being slowly absorbed as the mediastinal adenopathy regressed. General roentgen irradiation was continued field by field until, twenty days later, the fluid remaining in the right pleural cavity had almost disappeared (Fig. 8). One month afterward the fluid had been absorbed completely (Fig. 9). By this time the general lymphadenopathy had decreased greatly and the patient had recovered to such an extent that he could walk about town freely. He left the clinic to spend some time in

Europe. He failed to follow instructions about subsequent treatment and died the following winter.

If the disease is discovered early, it can be brought under control and kept so for a much longer time, and life may be prolonged several years. But even though in many cases the fatal issue cannot be postponed indefinitely, the symptoms can be relieved more or less completely during the interval. Sometimes, indeed, the clinical disturbances may be abolished so completely that the patient may be able to resume part or all of his usual activities and carry on until shortly before death. Inasmuch as the duration of the disease tends to be shorter in children and young adults and longer in persons of middle and old age, age is one of the factors which govern the effect of treatment, as far as the duration of such effect is concerned. This general rule, however, is subject to many exceptions; it is a tendency rather than a rule. But the more chronic the disease the longer the effect of irradiation on its manifestations tends to last.

Case 2.—A woman, age twenty-seven years, registered at the clinic July 28, 1921, complaining of enlarged lymph nodes on the right side of the neck. Her illness had begun early in 1920 when, shortly after extraction of an upper molar tooth, she had noticed a lump on the right side of the neck. Before 1918, however, she had had repeated attacks of tonsillitis and the tonsils had been removed in 1917 for this reason. Early in 1921 an acute respiratory infection, with cough and expectoration, lasted one month and was accompanied by further enlargement of the right cervical lymph nodes, and this was accompanied by general pruritus.

Examination disclosed slightly enlarged lymph nodes on both sides of the neck, but chiefly in the right supraclavicular space. Percussion of the thorax gave an abnormally broad area of mediastinal dullness, and a roentgenographic examination, July 29, 1921, showed a mediastinal tumor chiefly on the right side (Fig. 10). At biopsy a node from the right supraclavicular space yielded the pathologic diagnosis of Hodgkin's disease. The patient then received a course of rather general roentgen irradiation and a second roentgenographic examination of the thorax, September 28, 1921, showed that the mediastinal lymphadenopathic tumor had almost completely disappeared (Fig. 11). Nevertheless the patient was given a second course of treatment between September 28 and 30, 1921.

The patient remained free from any symptoms related to the lymphoblastomatous process until early in 1927, when the cervical nodes again enlarged, the face became puffy and congested, the respiration became difficult, and general itching caused distress and interfered with sleep. General examination disclosed bilateral supraclavicular, axillary, inguinal, mediastinal, and possibly also retroperitoneal lymphadenopathy, and a multitude of scratch marks corroborated the patient's complaint of pruritus. Roentgenographic examination of the thorax showed fresh tumefaction in the mediastinum, with secondary bronchiectasis of the lower lobe of the right lung. A course of roentgen-ray treatment, given between June 7 and 10, 1927, was followed by rapid improvement, and the patient has remained free from symptoms since that time. This may be regarded as an example of a rather chronic form of Hodgkin's disease and probably accounts for the more lasting influence of irradiation. The patient will undoubtedly die of the disease sooner or later; in the meantime she is well and able to carry on all her usual activities.

Another essentially lymphoid tumor in the mediastinum occurs chiefly in children. I refer to lymphoid hyperplasia of the thymus gland. It has never yet been determined what constitutes a normal thymus gland, as far as size is concerned, and the relationship of what may appear to be an abnormally large gland to the symptoms presented by the patient has not been clearly elucidated. It is undeniable, however, that irradiation causes the size of the hyperplastic gland to diminish rapidly, and the rate of regression again corresponds to the rate of destruction characteristic of normal lymphocytes. This tends to support the view of Hammar and others that the small round cells of the thymus gland are lymphocytes. Such knowledge can be utilized advantageously not only to treat a patient with thymic hyperplasia, but actually to distinguish such hyperplasia from other conditions which may simulate it.

Like epithelial tumors in general, the radiosensitiveness of epithelioma of the bronchus and esophagus is much lower than that of lymphoid tumors, because the sensitiveness of normal epithelium is much less than that of lymphocytes. It is but natural, therefore, that bronchial or esophageal neoplasms derived from epithelium should react less rapidly and less favorably than lymphoid growths. This is precisely what occurs in practice. In fact, there is a considerable gap in radiosensitiveness between the least sensitive of lymphoblastomas and the most sensitive epitheliomas. A small proportion of patients with tumors of this kind derive benefit to the extent of temporary inhibition of tumor growth and improvement in general condition for a number of months, but the improvement in the majority of patients is slight and lasts only a short time. In many patients the beneficial influence of the treatment is hardly perceptible. This applies to patients treated with roentgen rays of short wavelength generated at high voltage as well as to patients treated with radium. One possibility has not been adequately tested. On theoretic grounds it would appear that combined treatment with converging beams of highly filtered roentgen rays of short wave length and the more penetrating gamma rays of radium might lead to improved results in tumors of this kind. This possibility deserves a thorough trial. Sarcomas (except lymphosarcoma) do not often arise in the mediastinal structures, and such as occur in this region are usually metastatic. The radiosensitiveness of such growths depends on the variety of cell of which the tumor is composed. Academically speaking, the most sensitive variety of such neoplasms is represented by the chondrosarcoma, and the least sensitive by the myxosarcoma, but in practice the difference in radiosensitiveness between the two extremes is not great, and associated metastasis to the lungs often prevents the radiologist from accomplishing much.

The Mayo Clinic.